Remarks

This Response is to an Office Action mailed April 9, 2003.

I. Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1-7 are rejected under 35 U.S.C. Section 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter for which applicant regards as the invention. Office Action, page 2, paragraph 4. In particular, the Examiner stated that "claim 1 (and claims dependent thereon), the phrase "the functional symptoms of Parkinson's disease" lacks antecedent basis. The following remarks apply to the headings provided in the Office Action.

4A. Applicants have amended claim 1 to broaden the scope and to clarify the antecedent basis by reciting "a functional symptom of Parkinson's disease."

4B. Regarding the term "prophylaxis," Applicants respectfully submit that it is well known in the art that Parkinson's disease as well as other diseases can have variability over time in the severity of symptoms. In a state of remission, a particular functional symptom may not be present (e.g., ataxia), but the underlying condition (Parkinson's disease) is still present. Therefore, Applicants submit that an asymptomatic patient is not necessarily disease-free. Under such conditions, an asymptomatic patient can be treated with GPE to prevent symptoms from appearing. Thus, Applicants submit that the term "prophylaxis is not indefinite.

4C. Regarding the meaning of "a functional symptom of Parkinson's disease," Applicants direct the Examiner's attention to the specification, page 4, which states:

> [Parkinson's disease] is a chronic and progressive motor system disorder and is distinguished by a **tremor at rest, muscular rigidity, a slowness of movement initiation and movement execution** and a **mask-like appearance to the face**. Emphasis added.

Thus, Applicants submit that the specification provides sufficient definition of the term "a functional symptom of Parkinson's disease" and thus, that the claims are not indefinite.

4D. Regarding the term "GPE", Applicants herein describe GPE to mean the tripeptide, Gly-Pro-Glu. This definition finds support in the specification on page 3, line 12 and page 4 line 22.

4E. Regarding the terms "analog of GPE" and "mimetic of GPE," Applicants have amended the claims to exclude those terms.

4F. Regarding claims 1, Applicants respectfully assert that the step of "**increasing** the effective amount of GPE" renders the claim a method claim. [Emphasis added.] Because the remainder of the claims depend from claim 1, all the claims in this application are method claims. Applicants submit that the term "increasing" is a method step well known in the art and is not indefinite. The Examiner is requested to provide an Affidavit/Declaration including evidence that the term "increasing" is not a method step.

II. Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1-7 are rejected under 35 U.S.C. Section 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (LACK OF WRITTEN DESCRIPTION). Office Action, page 4, paragraph 6.

Claims 1-7 are rejected under 35 U.S.C. Section 112, first paragraph, because the specification, "while being enabled for a method of protecting dopaminergic neurons against death resulting from Parkinson's disease using a neuroprotective amount of Gly-Pro-Glu as described in the examples; the specification does not reasonably provide enablement for the scope of analogs/mimetics/prodrugs of Gly-Pro-Glu to treat all "functional symptoms of Parkinson's disease as presently claimed"

Applicants have amended claim 1 to exclude the terms "analog" and "mimetic" and thus submit that the metes and bounds of the claims are not indefinite. Moreover, Applicants respectfully submit that the scope of claims is not necessarily limited to the examples in the specification and that working examples are not always necessary for enablement (see *In re Wands*). For example, Applicants submit that it is known in the art that certain peptides can be cleaved by peptidases or proteases to result in formation of shorter peptides. In particular, it is known that IGF-I can be degraded to produce des(1-3) IGF-I and the N-terminal tripeptide, GPE. See specification at page 3, second paragraph. Applicants therefore assert that the term "prodrug" of GPE includes peptides, including but not limited to IGF-I, that, upon cleavage result in

formation of GPE. Thus, in contrast with the Examiner's point on page 9, lines 11-13 of the Office Action, Applicants have provided description of a "prodrug" of GPE, namely IGF-I.

Applicants respectfully submit that the Examiner's reliance on *University of California v. Eli Lilly (Lilly)* is misplaced. In *Lilly*, the issue was whether an **undisclosed** peptide sequence (having one additional N-terminal amino acid included in human insulin) was included within the meaning of a peptide sequence (e.g., rat sequence) lacking that one additional amino acid. Although the Court held that "mammalian insulin" was not described with sufficient specificity to indicate possession of "human insulin," in the instant case, all "prodrugs" of GPE contain the exact sequence, GPE. Applicants further submit that GPE can be detected and measured using methods that are routine in the art.

Likewise, the Examiner's reliance of Judge Lourie's comments is misplaced. The instant claims are directed to methods of treating "a functional symptom of Parkinson's disease by increasing the effective amount GPE." Applicants are not claiming any other mechanism of action, and in light of the specificity with which Applicants have defined "GPE", the claims do not lack written description.

Applicants also note that the Written Description Guidelines do not have the force of law (see MPEP 2163). "The Guidelines do not constitute substantive rule-making and hence do not have the force and effect of law." Applicants note that the claim term "prodrug of GPE" was present in the claims as originally filed, is not new matter and thus, is entitled to "a strong presumption that an adequate written description of the claimed invention is present when the application is filed (see *In re Werthheim*), MPEP 2163 I.A. (page 2100-156 August 2001). Thus, Applicants submit that the term "prodrug of GPE" as commonly understood in the art defines such materials as those that upon proteolysis, produce the product (namely GPE), and therefore meets the standard articulated in *Amgen v. Chugai* (MPEP 2163) by providing description of "whatever characteristics sufficiently distinguish it." In the instant case, by producing GPE.

Regarding lack of enablement, stated on Page 8, paragraph 7 of the Office Action, Applicants point out that the Examples in the specification provide direct evidence, *in vivo*, of the efficacy of the claimed invention. First, Applicants remind the Examiner that "a functional symptoma" of Parkinson's Disease as defined in the specification are: "a tremor at rest, muscular

rigidity, a slowness of movement initiation and movement execution and a mask-like appearance to the face."

Thus, Applicants respectfully submit that discovering a positive correlation between "increasing GPE" and improvement in any "functional symptom" as described above and in the specification, is sufficient to teach one of ordinary skill how to make and use the invention for the scope of the claims, thereby demonstrating enablement. The following paragraphs provide descriptions of working examples supporting enablement.

Experiment 4 (page 16 et seq) of the specification provides sufficient demonstration of efficacy of GPE in an art-recognized model of Parkinson's disease, namely rats subjected to treatment with 6-hydroxy dopamine (6-OHDA). Several functional symptoms of Parkinson's disease were tested using art-recognized tests: rotation test, step time test, step length test, and the presence and frequency of adjusting steps. Each of the tests is a test of at least one functional symptom, namely tremor at rest, muscular rigidity or slowness of movement initiation and movement execution.

Figures 7-10 depict graphs of results of the above tests, and without exception, demonstrate that increasing GPE decreases the frequency of spontaneous rotations (Figure 7), increases speed of locomotion (Figure 8), increases step length (Figure 9) and increases the number of adjusting steps (Figure 10). Each of the above results correlate with "a functional symptom of Parkinson's disease" and show that treating "a functional symptom of Parkinson's disease" by "increasing the effective amount of GPE" is effective. Applicants submit that the specification as filed supports the scope of the instant claims without undue experimentation and with a reasonable likelihood of success.

In light of the amendment of the claims, Applicants submit that all of the compounds claimed have a common structural feature, namely that they are either GPE or a prodrug of GPE that produces GPE. Thus, Applicants respectfully submit that the arguments presented on page 10 of the Office Action do not render the claims non-enabled.

Furthermore, as mentioned above, the efficacy of "increasing the effective amount of GPE" has been directly demonstrated *in vivo* in a system recognized to be predictive of human Parkinson's disease, namely rats treated with 6-OHDA. The Examiner has provided no evidence that the rat/6-OHDA system is not predictive of human Parkinson's disease. If the Examiner is

aware of any such evidence, Applicants respectfully request the Examiner to provide an Affidavit/Declaration including such evidence.

Issues relating to drug delivery and pharmacokinetic properties are not relevant to *in vivo* demonstration of the utility of "increasing the effective amount of GPE" to treat "a functional symptom of Parkinson's disease." The fact that the animals survived *in vivo* treatment indicates that the drugs were not lethal. Moreover, Applicants note that it is not a requirement of patentability that a treatment must have no toxicity. Although Applicants did not describe toxic effects of "increasing the effective amount of GPE", Applicants submit that it is well known that the Food and Drug Administration (FDA) is charged with evaluation of therapeutic and toxic properties (effective doses and toxic doses and effects) of all compounds approved for human use. The PTO is not charged with that responsibility and thus, Applicants respectfully assert that consideration of toxicity, if present, is not relevant to patentability of the claims under the instant circumstances.

Applicants therefore respectfully submit that the current claims are fully described and fully enabled, and urge the Examiner to reconsider the rejections and find the claims patentable under 35 U.S.C.§112, first and second paragraphs.

Rejections Under 35 U.S.C. §102

Claims 1-7 are rejected under 35 U.S.C. 102(a, b) as being anticipated by Gluckman, WO 93/02695 (the "'695" patent). The Examiner stated: "Gluckman teaches administering IGF-1. . to treat CNS injuries which are "a consequence of Parkinson's disease .... The disclosure of "Functional symptoms" (e.g., hypoxia/ischemia/trauma/demyelination" of Gluckman are within the scope of "functional symptoms of Parkinson's disease" as presently (and broadly) claimed." Office Action, pages 13-bridging page 14.

Applicants request the Examiner's assistance in identifying particular locations within the '695 patent that the Examiner believes supports the rejection of the instant claims. Applicants can identify no disclosure that anticipates "A method for treating a functional symptom of Parkinson's disease" as defined in the instant specification. In particular, Applicants can find no disclosure of "tremor at rest, muscular rigidity, a slowness of movement initiation and movement execution" or

"a mask-like appearance to the face." Therefore, the '695 patent does not teach all limitations of the claim with as much precision as claimed, and thus is neither enabling nor capable of anticipating the instant claims. Applicants therefore urge the Examiner to reconsider the rejections and find the claims allowable over the '695 patent.

Claims 1-7 are rejected under 35 U.S.C. 102(a, e) as being anticipated by Gluckman et al, U.S. Patent No. 6,187,906 (the "'906" patent).

As with the '695 patent described above, Applicants can find no disclosure in the '906 patent of treatment of "a functional symptom of Parkinson's disease" as defined in the instant specification. Thus, there is no disclosure of effective treatment of "tremor at rest, muscular rigidity, a slowness of movement initiation and movement execution and a mask-like appearance to the face." Without such disclosure, the '906 patent cannot anticipate the instant claims. Applicants therefore request the Examiner to reconsider the rejections and find the claims patentable under 35 U.S.C.§102.

Rejections Under 35 U.S.C. §103

Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Noble et al. U.S. Pat. No. 5,762,922 (the "'922" patent). The Examiner stated: "[t]he selection of growth factors (or IGF-1) (e.g. which qualify as analogues/mimetics of GPE) which treat Parkinson's would have been prima facie obvious to one of ordinary skill in the art since the selection of growth factors and Parkinson's represent preferred embodiments as evidenced by the patent claims. Office Action, page 14, paragraph 11.

According to the MPEP:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one or ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a **reasonable expectation of success**. Finally, the prior art reference (or references when combined must teach or suggest **all the claim limitations**. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and **not based on applicant's disclosure**. MPEP 2142. [Emphasis added.]

Applicants note that the '922 patent is directed toward combinations of agents that include a growth factor and an agent that increases intracellular glutathoine for treating a condition characterized by "insufficiency of a particular cell type." However, Applicants can find no teaching or suggestion of treating "a functional symptom of Parkinson's disease" as defined in the instant specification, namely, "tremor at rest, muscular rigidity, a slowness of movement initiation and movement execution and a mask-like appearance to the face." Applicants submit that based solely on Noble, one would not be motivated to use GPE to treat "a functional symptom of Parkinson's disease" as claimed. At best, one would be motivated to "try" to find out whether IGF-1 might be useful. There could be no motive, based on Noble, to "try" to use GPE for that purpose. Furthermore, the Examiner has produced no evidence that there would be a reasonable expectation of success of arriving at the Applicants' appreciation that "increasing the effective amount of GPE" would be of benefit to treat "a functional symptom of Parkinson's disease." Thus, Applicants respectfully submit that the '922 patent did not teach or suggest all the limitations of the instant claims, and therefore cannot render them obvious. Thus, according to MPEP cited above, no *prima facie* case of obviousness has been made. If the Examiner is aware of any evidence of such a reasonable expectation of success, Applicants respectfully request the Examiner to provide an Affidavit/Declaration presenting such evidence.

Claims 1-7 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 6,187,906 (the "'906" patent).

Applicants submit that as with the '922 patent described above, the '906 patent does not teach or suggest all the limitations of the instant claims without undue experimentation and a reasonable likelihood of success. Applicants can find no teaching or suggestion of "a functional symptom of Parkinson's disease" could be treated by "increasing the effective amount of GPE" as in the instant claims. In particular, there is no teaching that "a functional symptom of Parkinson's disease" includes "tremor at rest, muscular rigidity, a slowness of movement initiation and movement execution and a mask-like appearance to the face." Thus, absent the disclosure in the instant specification, nothing in the '906 patent taught or suggested treating "a functional symptom of Parkinson's disease" as disclosed in the instant application and as claimed with a reasonable likelihood of success. If the Examiner is aware of evidence in the prior art that renders the claims obvious, Applicants invite the Examiner to present such evidence in an Affidavit/Declaration.

There are no fees due with this communication. However, the Commissioner is authorized to charge any underpayment or credit any overpayment to Deposit Account No. 06-1325 for any matter in connection with this response, including any fee for extension of time, which may be required.

Respectfully submitted,

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Date: July 8, 2003

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